COVID-19 Neurologic Consequences

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Conflict of Interest

- None

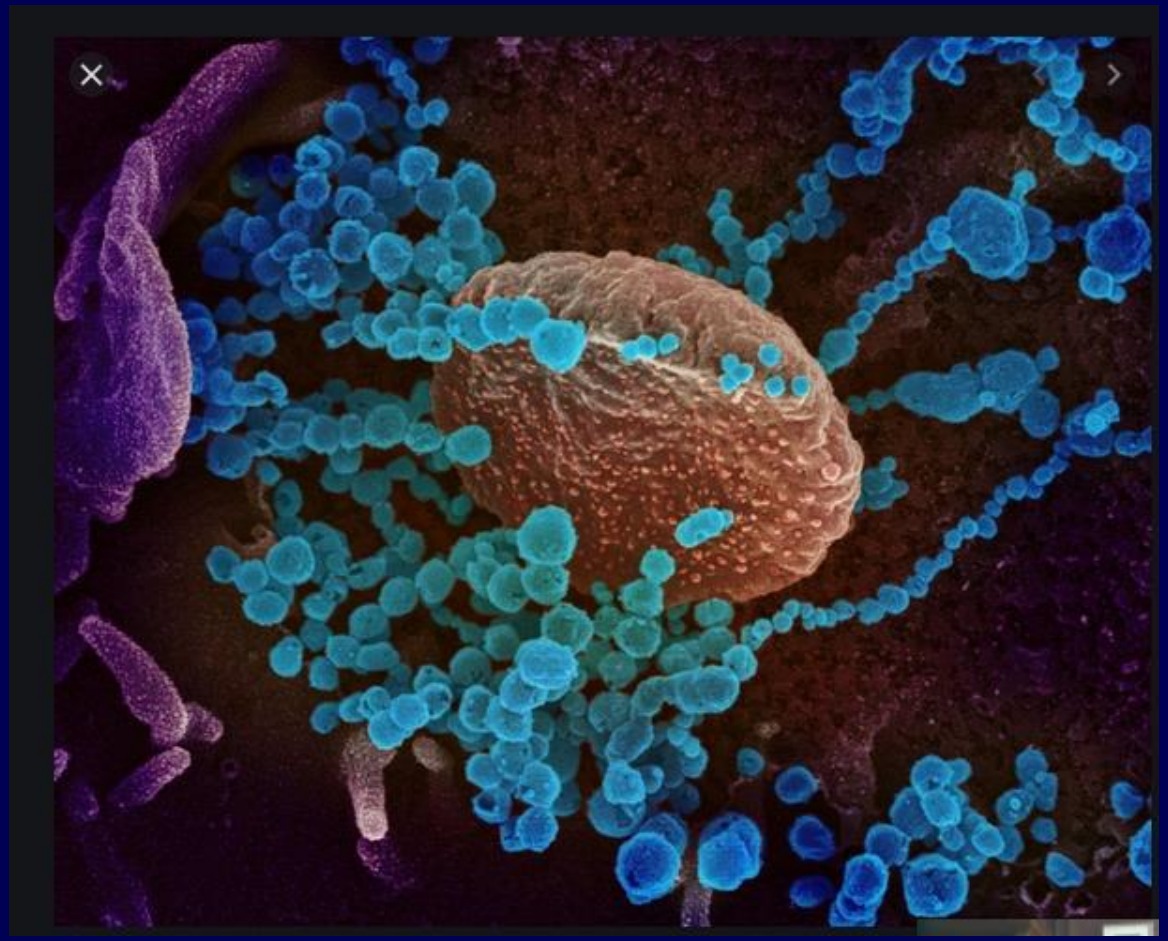
Educational Objetives

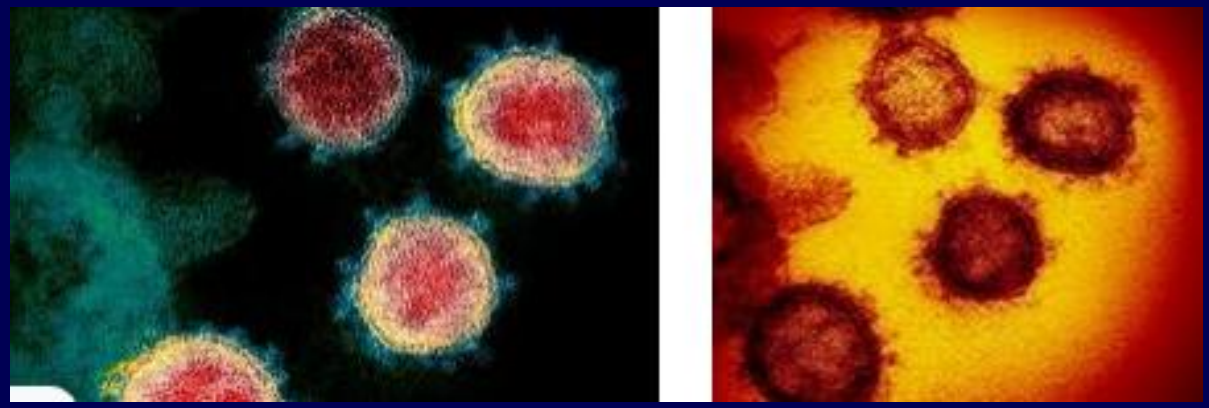
- To understand the central and peripheral nervous system pathophysiology of Covid-19 infection
- To understand the main acute manifestations and complications of Covid-19
- To understand the neurologic complications of the Post-Covid Syndrome (Long Covid)

Content

- 1. The SARS-CoV-2 Virus
- 2. Pathophysiology and Neuropathophysiology
- 3. Acute Manifestations and Complications
- 4. Neurologic complications of the Long Covid Syndrome
- 5. Conclusions

1. SARS-CoV-2 Virus





CORONAVIRUS

- According to Henry , the name “coronavirus,” from the Latin corona(crown), was coined in 1967 by June Almeida based on ultrastructural images resembling the solar corona that she obtained of human cold viruses and the avian infectiou bronchitis virus enteric diseases

- J.D.Almeida, D.A.Tyrrell. J.Gen.Virol.1(1967)175–178.

CORONAVIRUS: Original Contribution

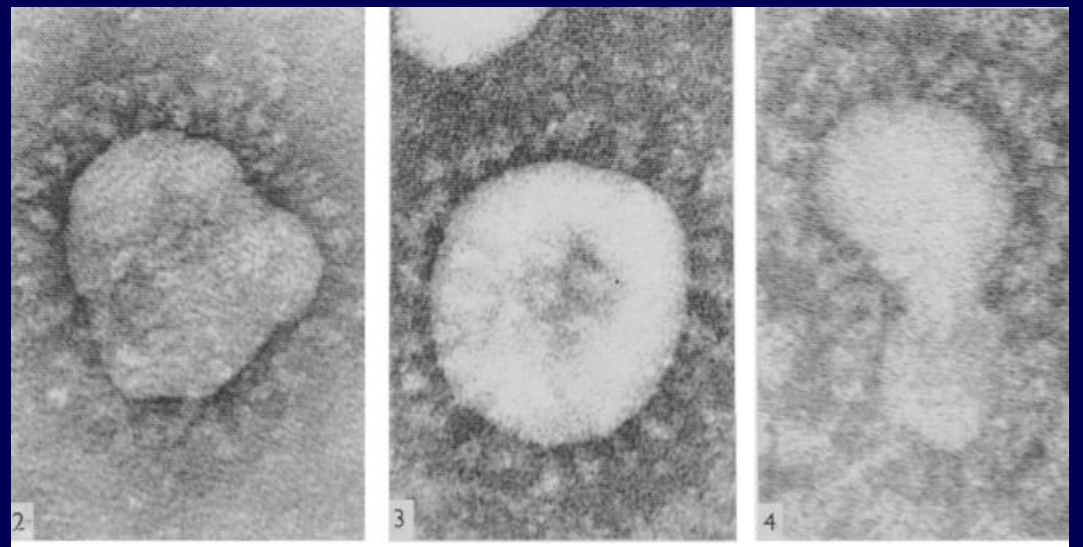
J. gen. Virol. (1967), **1**, 175–178
With 2 plates
Printed in Great Britain

The Morphology of Three Previously Uncharacterized Human Respiratory Viruses that Grow in Organ Culture

By JUNE D. ALMEIDA
Department of Medical Microbiology, St Thomas's Hospital Medical School, London, S.E.1

AND D. A. J. TYRRELL
Common Cold Research Unit, Medical Research Council, Salisbury, England

(*Accepted* 28 *November* 1966)



J. D. ALMEIDA AND D. A. J. TYRRELL (*Facing p.* 178)

- J.D.Almeida, D.A.Tyrrell. J.Gen.Virol.1(1967)175–178.

CORONAVIRUS

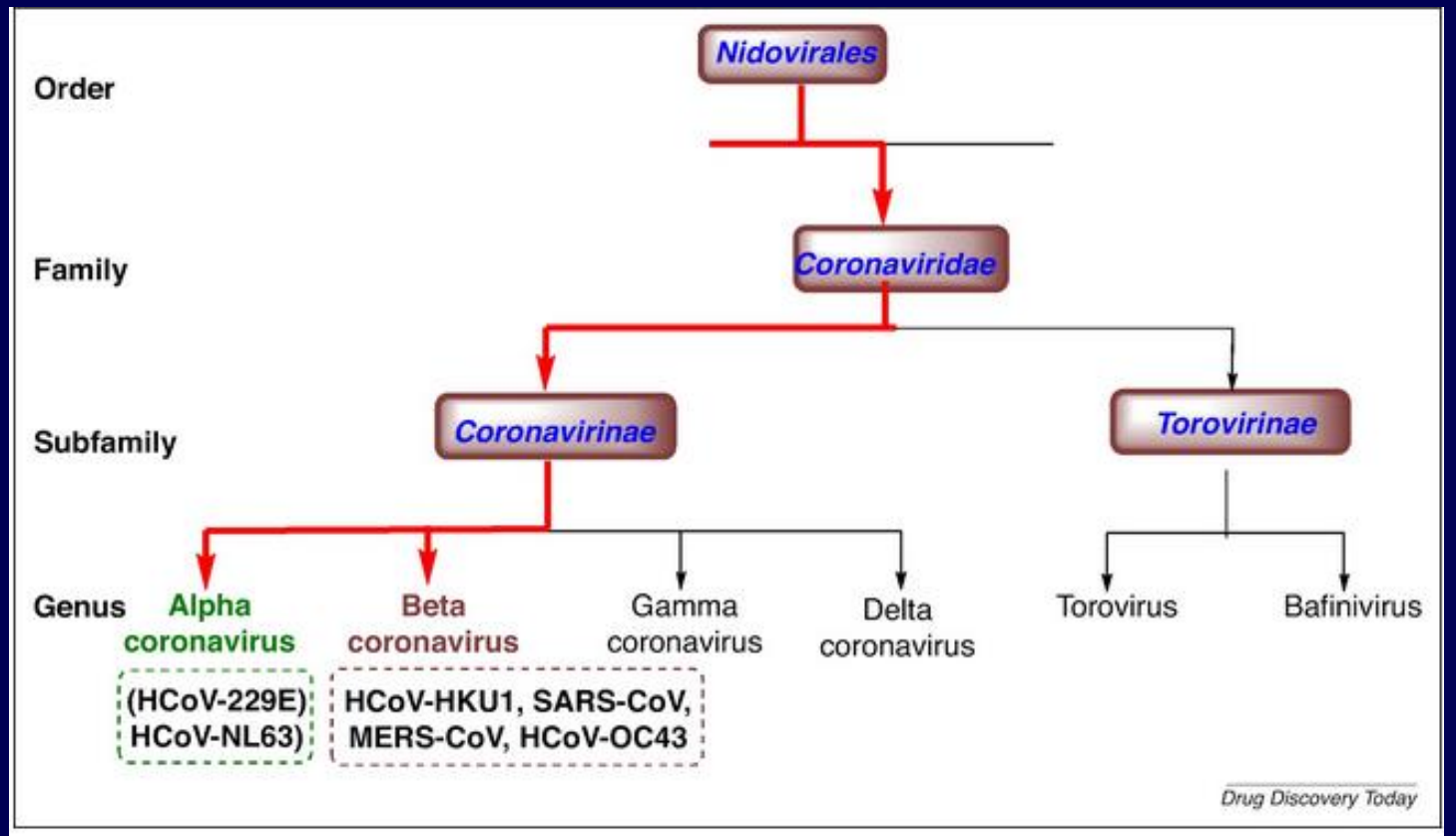
- The coronaviruses (CoV) are members of the Coronavirinae sub-family. The Torovirinae plus the coronaviruses comprise the Coronaviridae family in the order Nidovirales

- Cui et al. Nat.Rev.Microbiol.17(2019)181–192.

COV

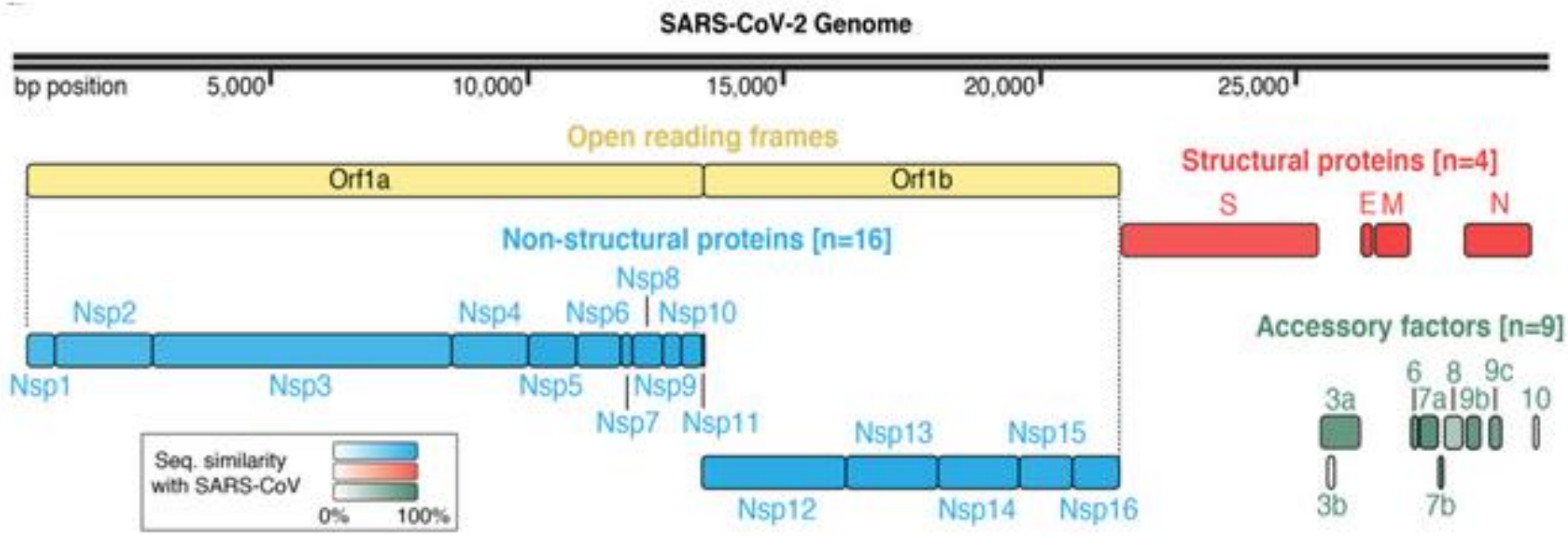
- CoVs are classified in four different genera: alpha, beta, gamma, an delta-CoV according to their phylogenetic links and genomic structures. The Coronaviridae members MERS-CoV, SARS-CoV-1, and SARS-CoV-2 all belong to the beta-coronavirus(β-CoV)genus and share highly homologous genomic sequences

Clasification



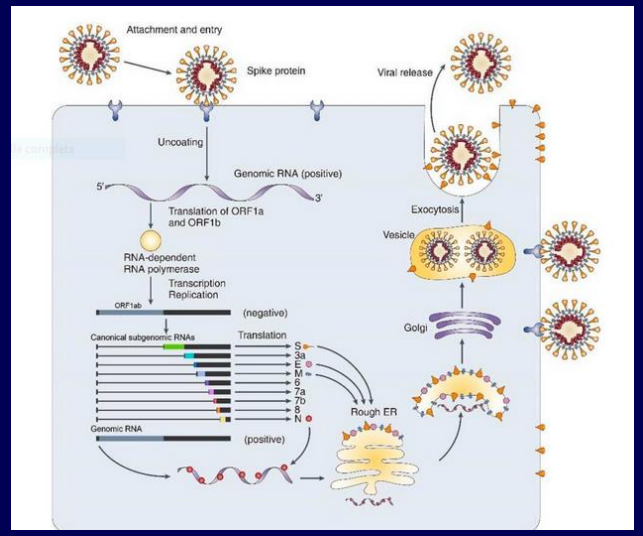
Schematic of the taxonomy of Coronaviridae family of viruses as per ICTV classification, highlighting coronaviruses known to infect humans. From Pillaiyar et al., Drug Discovery Today, 2020.

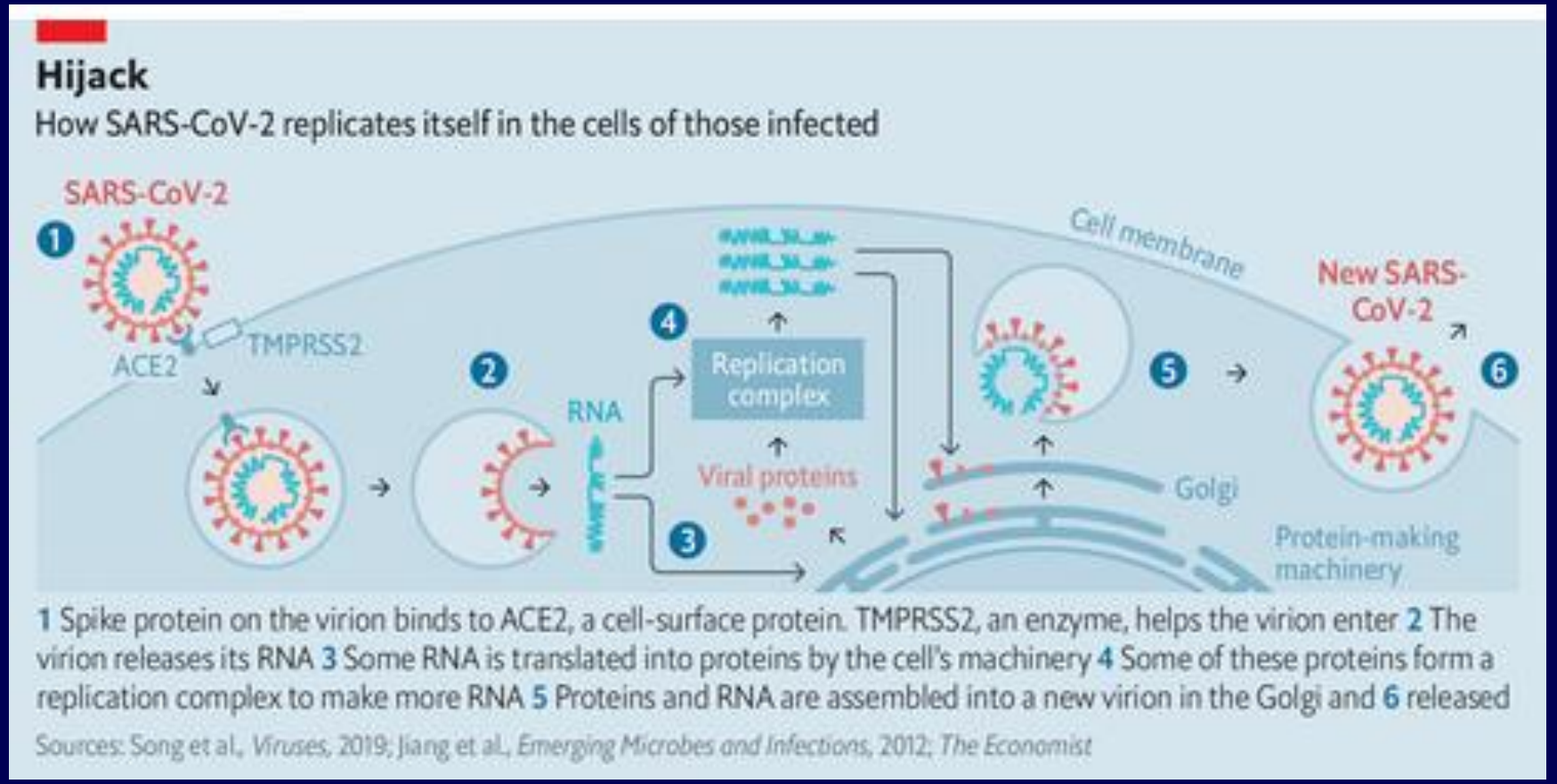
Genomic Organization



SARS-CoV-2 genomic organization and encoded proteins (Lu et al., Lancet 2020; genome assembly data). Figure from Gordon et al., Nature 2020.

Replication Mechanism





SARS-CoV-2 Structure

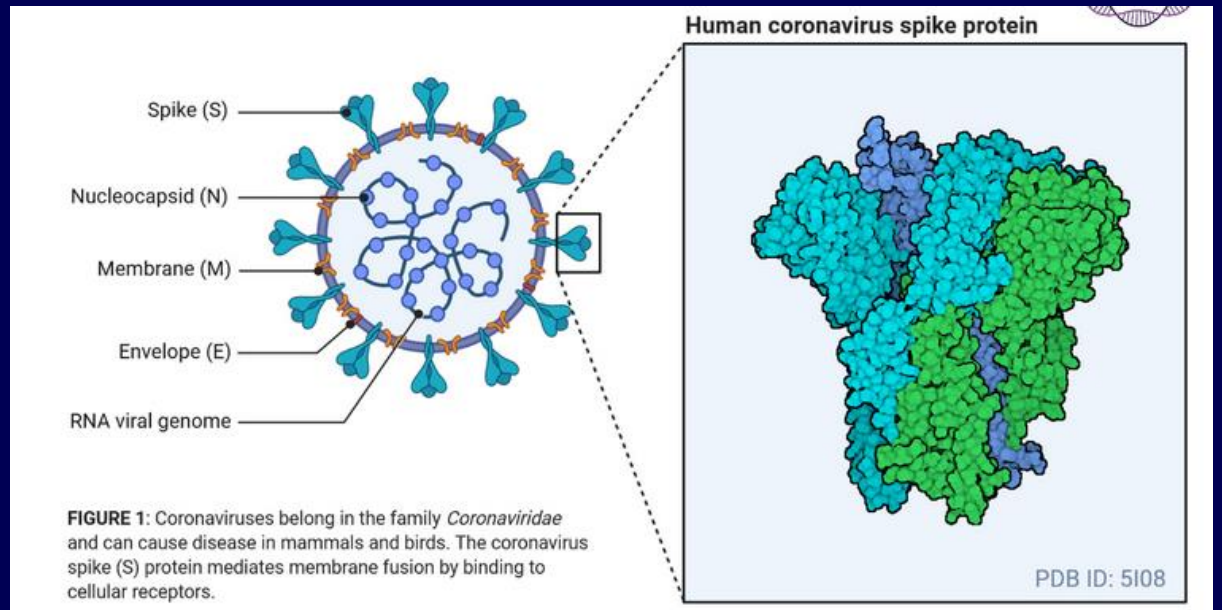
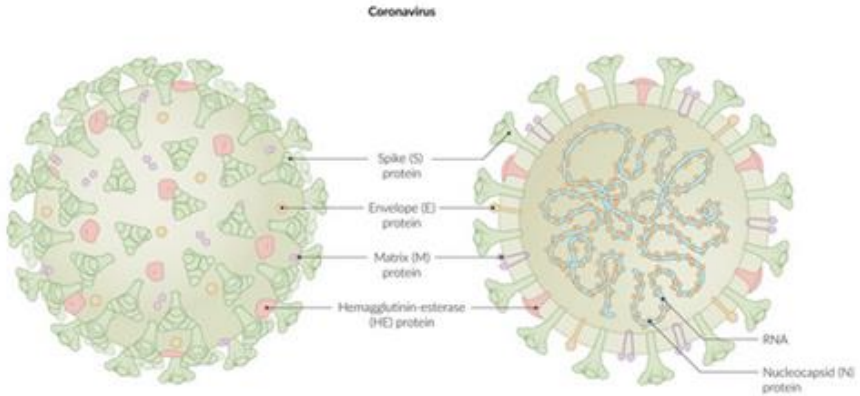


FIGURE 1: Coronaviruses belong in the family *Coronaviridae* and can cause disease in mammals and birds. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors.

Figure: Structure of SARS-CoV-2, created with biorender.com

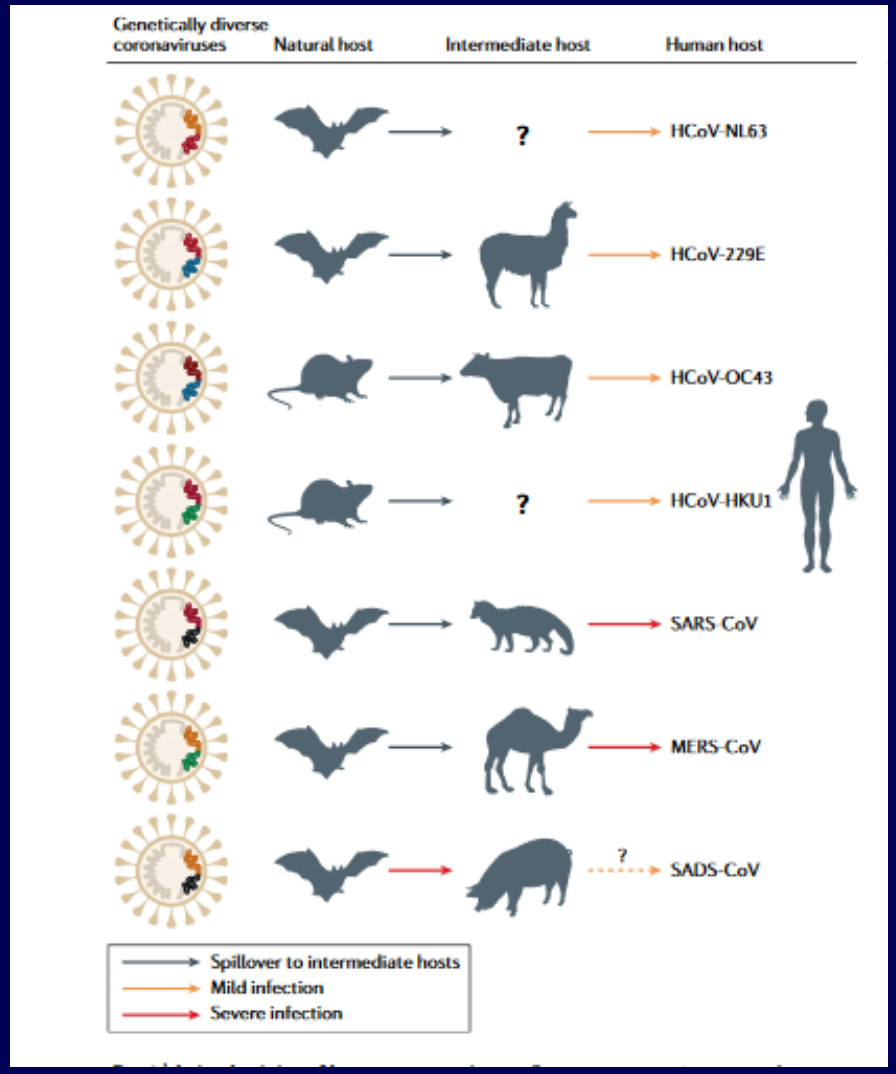
Structural Protein	Protein Function and Features
Nucleocapsid protein (N)	• Binds with RNA genome to make helical ribonucleoprotein
Membrane protein (M)	• Transmembrane envelope protein • Determines shape of viral envelope
Envelope protein (E)	• Interacts with M protein to form viral envelope • Important for virus infectivity
Spike protein (S)	• Binds to host cell receptors to facilitate entry into host cells • Targeted by host neutralizing antibodies

Structural proteins of coronaviruses and their functions. Summarized from Fields, Knipe, Howley, Fields Virology 6e 2013.



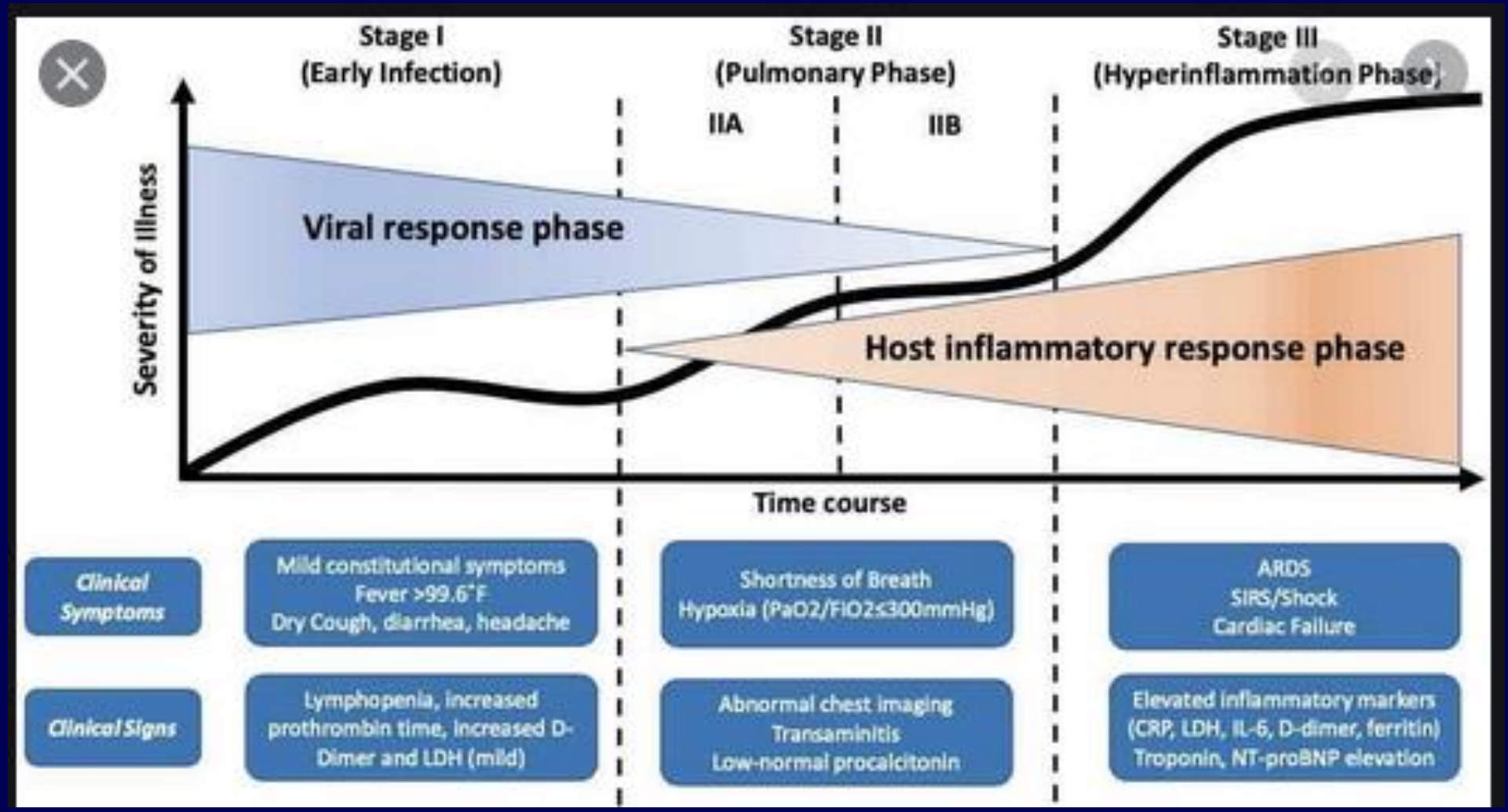
Coronavirus structure. Schematic showing major structural proteins of the coronavirus virion. From AMBOSS.

CORONAVIRUS ORIGEN

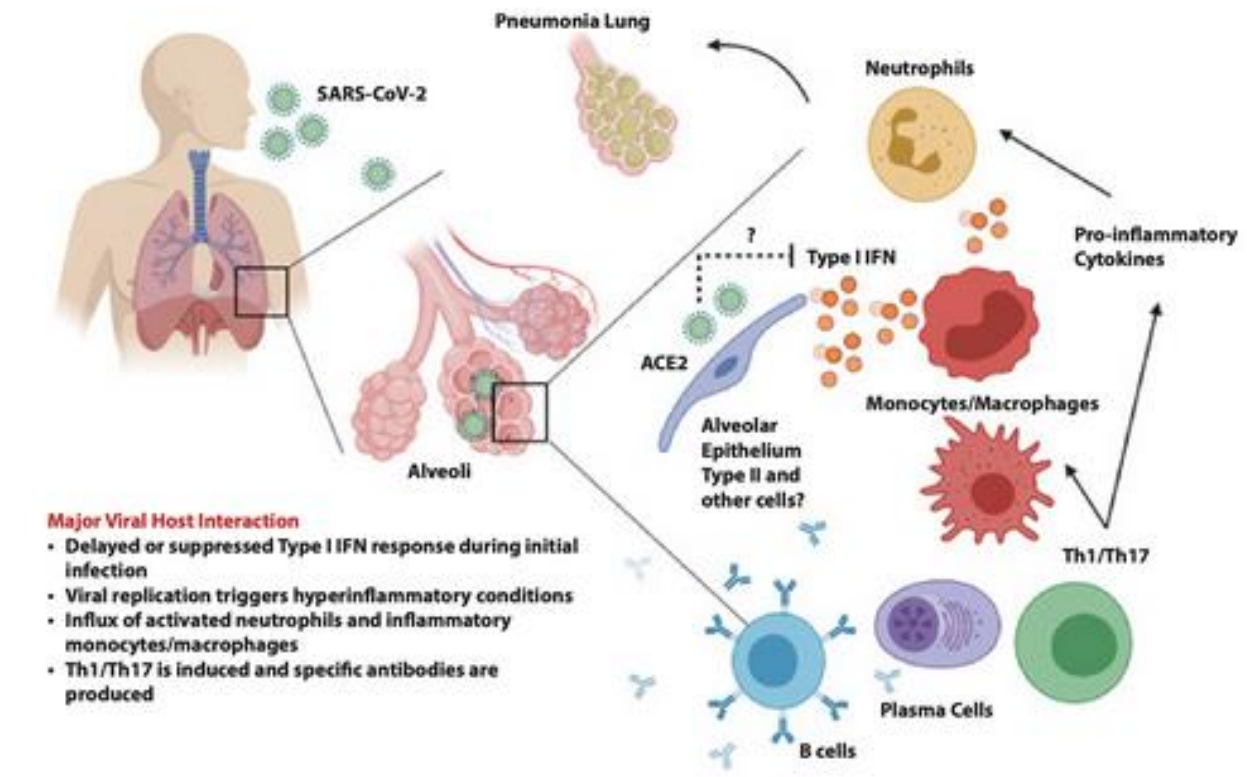


» Cui et al. Nat.Rev.Microbiol.17(2019)181–192.

2. Pathophysiology



Immune Response

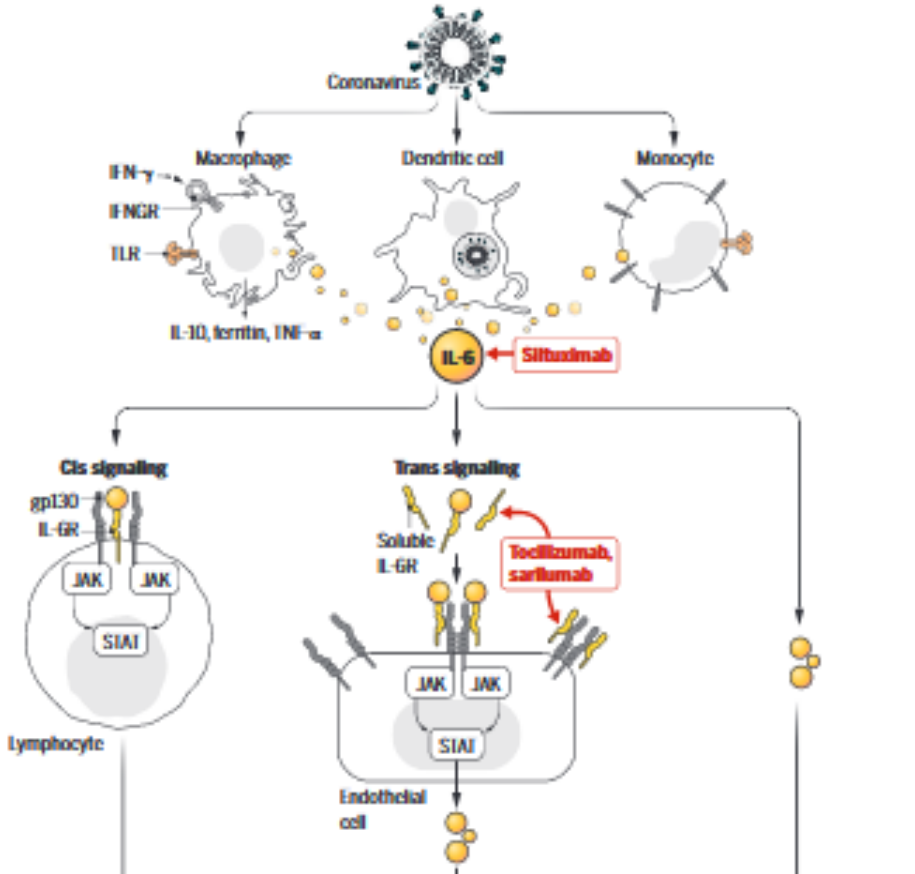


(Prompetchara et al., APJAI 2020)

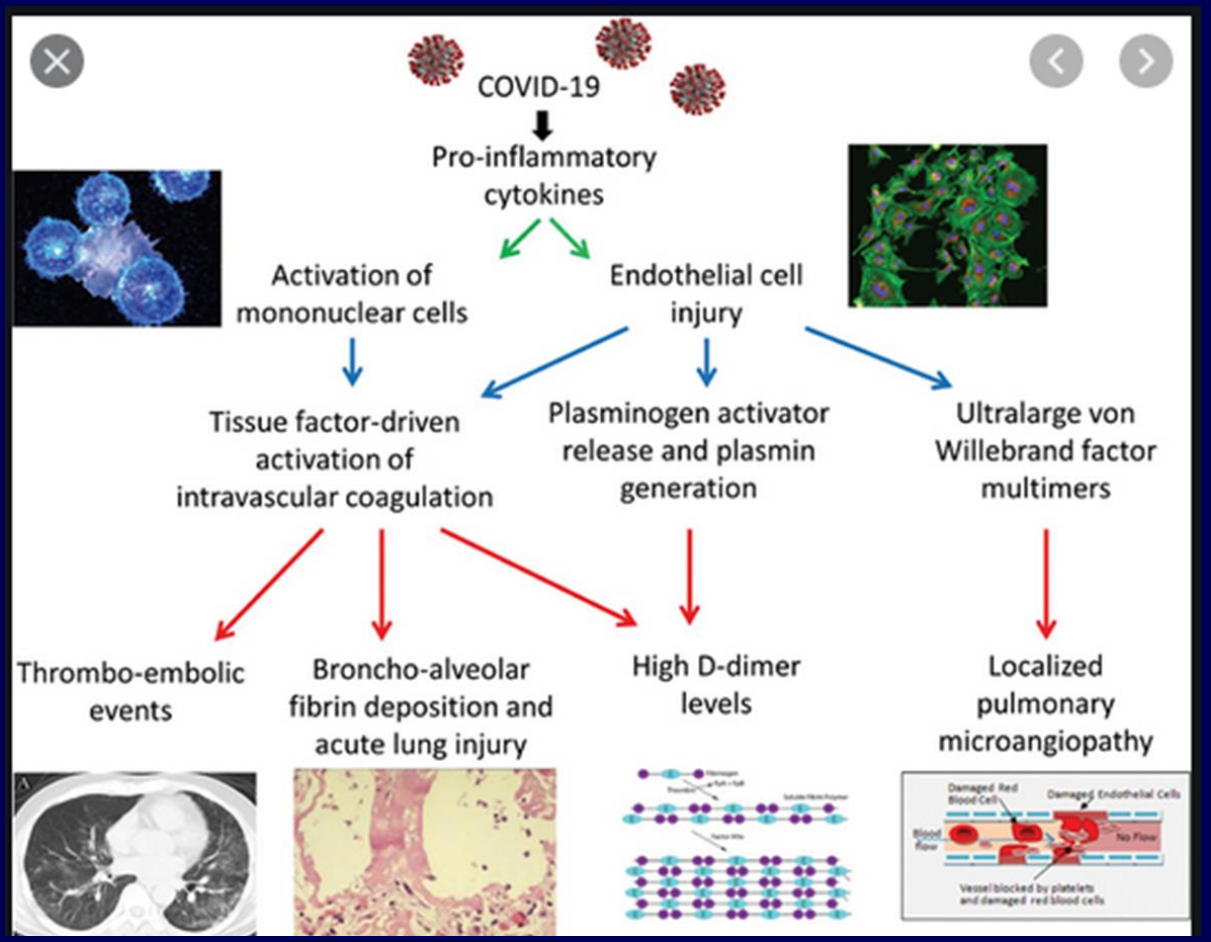
Cytokine release syndrome

Pathways leading to cytokine release syndrome

Coronavirus infection results in monocyte, macrophage, and dendritic cell activation. IL-6 release then instigates an amplification cascade that results in cis signaling with T_H17 differentiation, among other lymphocytic changes, and trans signaling in many cell types, such as endothelial cells. The resulting increased systemic cytokine production contributes to the pathophysiology of severe COVID-19, including hypotension and acute respiratory distress syndrome (ARDS), which might be treated with IL-6 antagonists such as tocilizumab, sarilumab, and siltuximab.

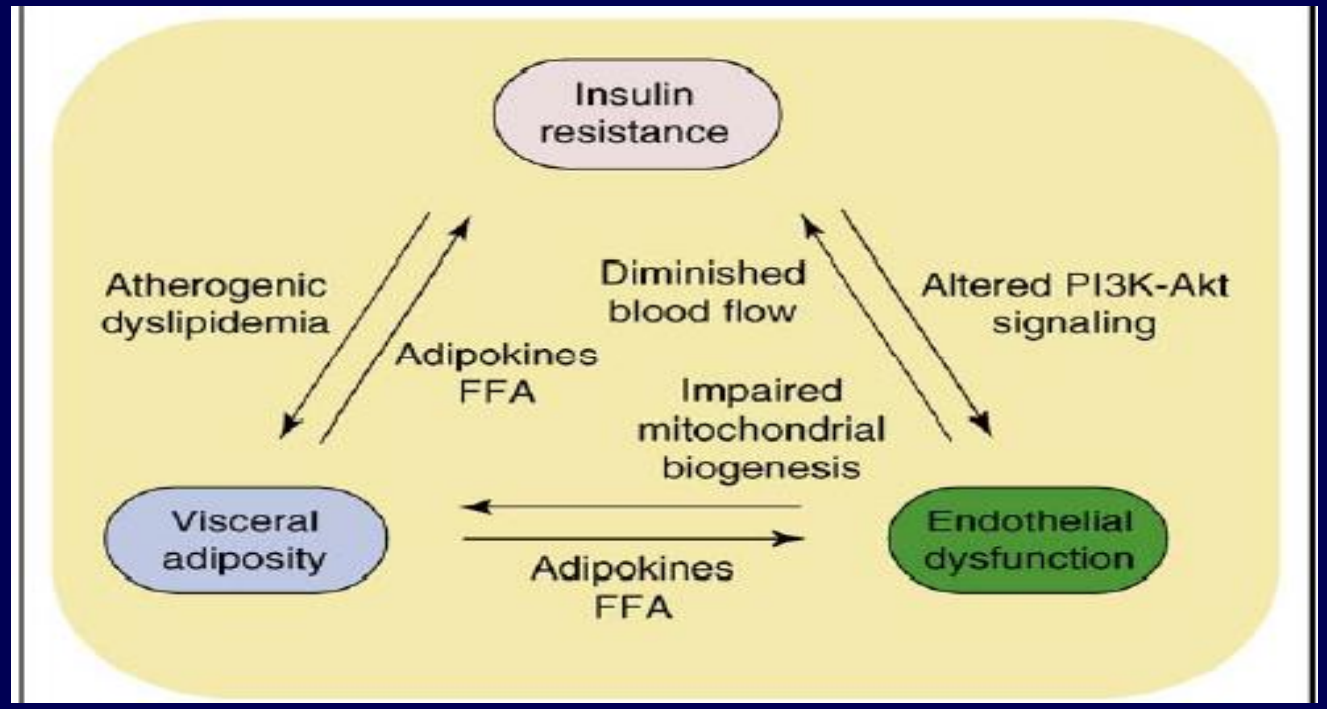


C3, complement 3; CRP, C reactive protein; IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF-α, tumor necrosis factor-α; TLR, toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.



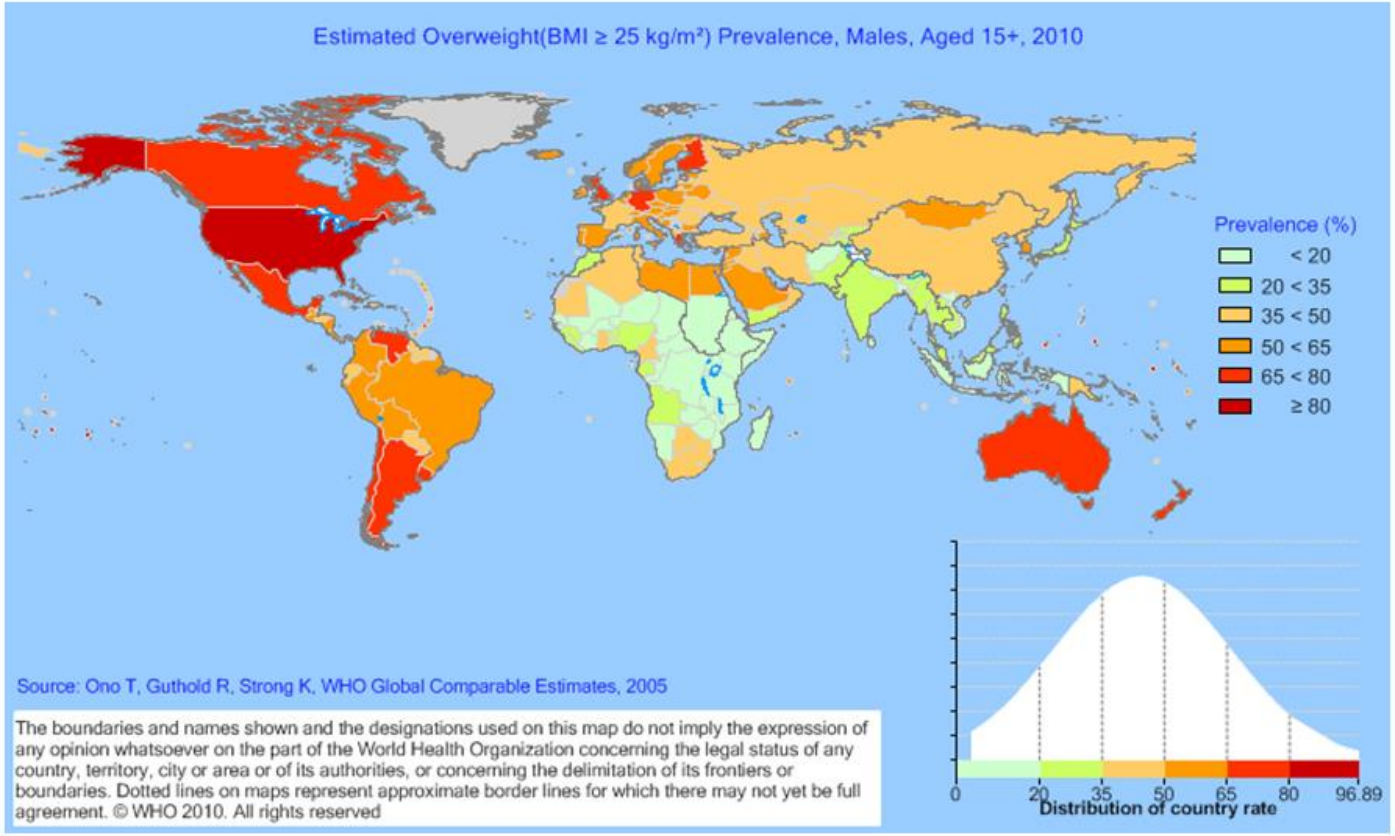
Metabolic Syndrome y la eNOS

- Metabolic Syndrome: Visceral adiposity, Insulin resistance and Endothelial dysfunction



- Huang et al Stem Cells Dev. 2010 Oct;19(10):1617-26.

Estimated overweight & obesity (BMI ≥ 25kg/m^2) prevalence, Males, Aged 15+, 2010



World Health Organization

Endothelial dysfunction

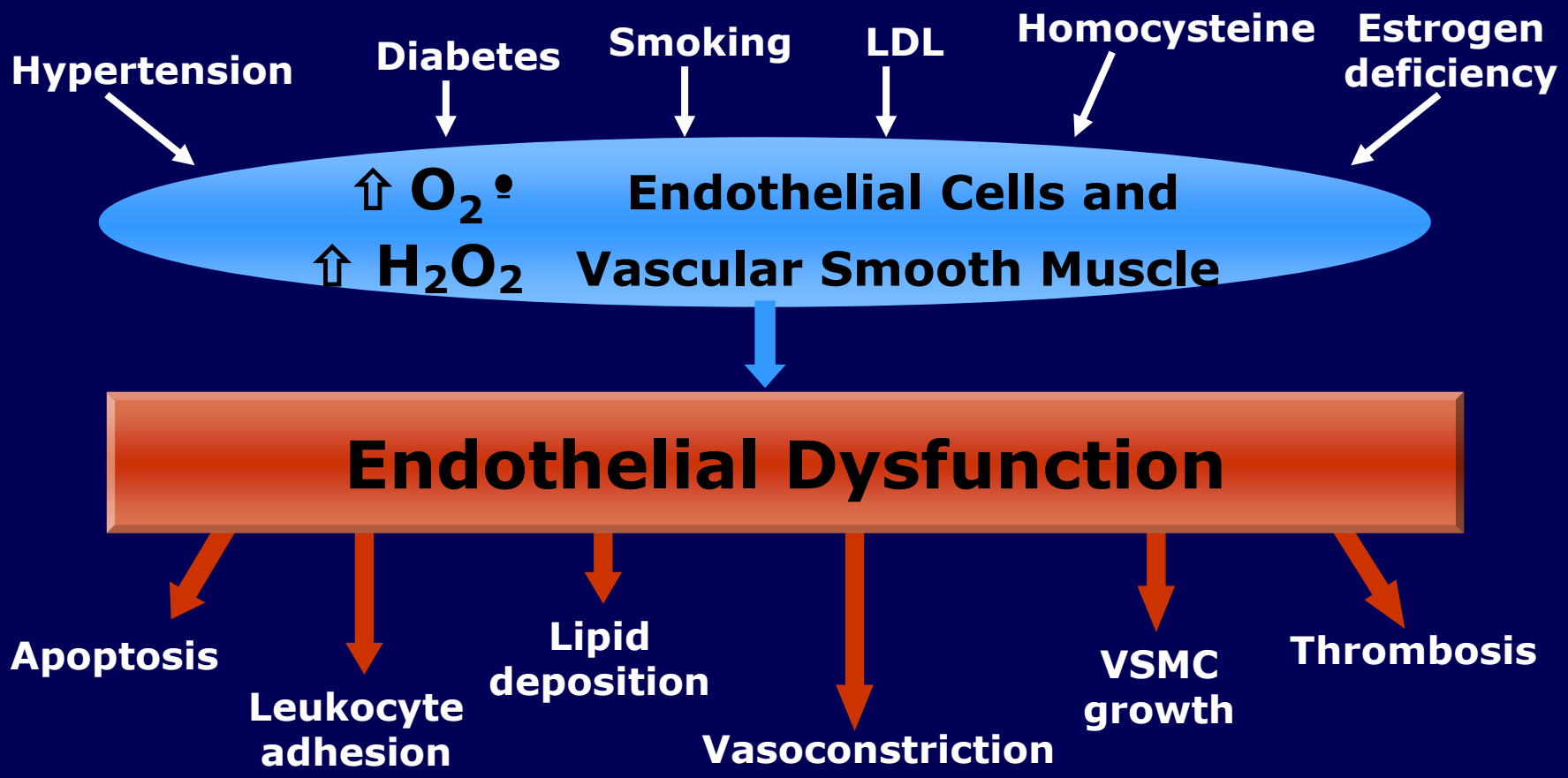
- Endothelial dysfunction represents a reduction on the nitric oxide-dependent-vascular dilatation and can be described as an imbalance between vasodilatation and vasoconstriction produced by the endothelium and predict disease with family history of essential hypertension or risk factors for atherosclerosis

Moncada S, Higgs A, New England Journal of Medicine 1993;329:2002–2012.

Moncada S, Higgs EA. Handbook of Experimental Pharmacology. 2006; (176 Pt 1):213- 254.

Moncada S, Higgs EA. British Journal of Pharmacology. 2006;147 (Suppl 1):S193-201.

Oxidative Stress: Endothelial Dysfunction and CVD



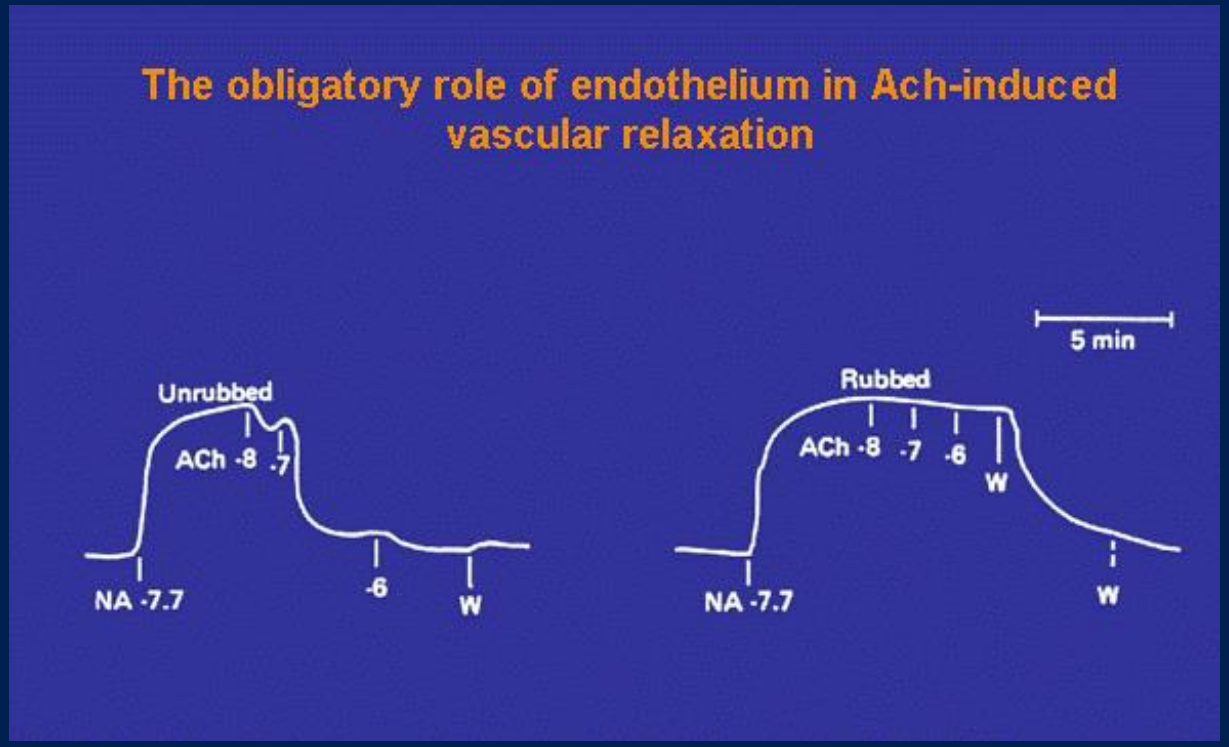
Nitric Oxide

- Nitric oxide (NO) has a fundamental role in neurovascular homeostasis. In endothelial cells, NO regulates vascular tone, platelet aggregation, leukocyte adhesion, and endothelial junctional permeability.

Moncada S, Higgs EA. Handbook of Experimental Pharmacology. 2006; (176 Pt 1):213- 254.

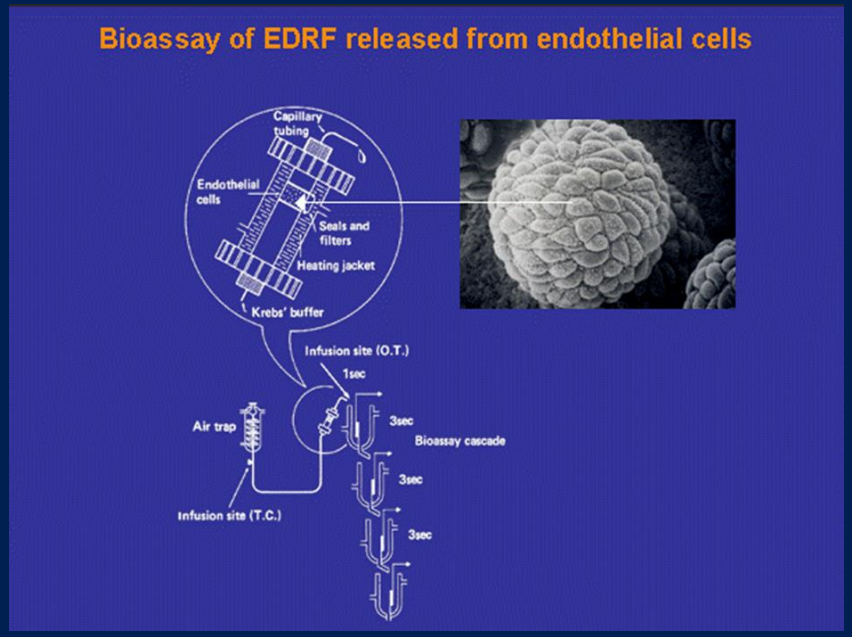
Moncada S, Higgs EA. British Journal of Pharmacology. 2006;147 (Suppl 1):S193-201.

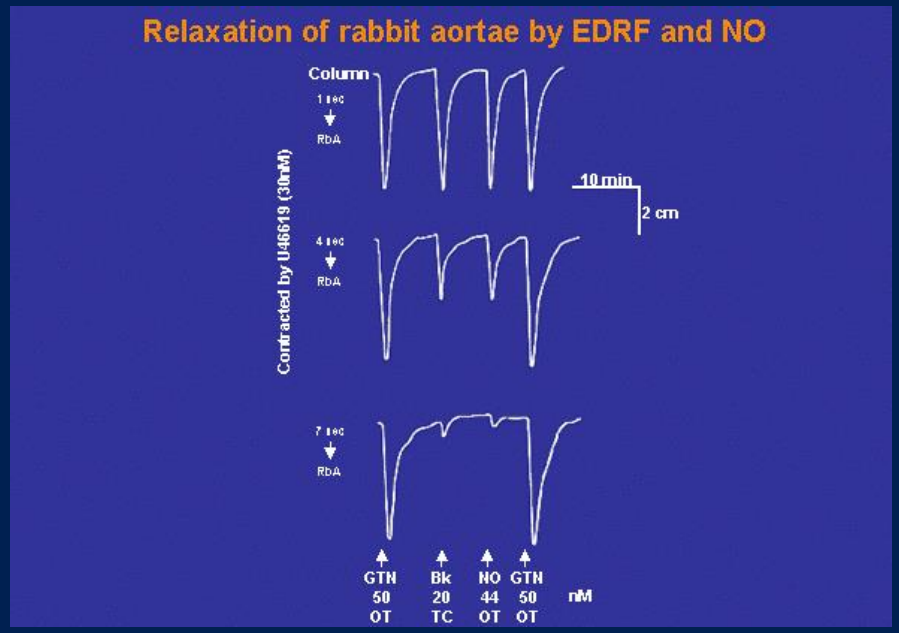
EDRF (Endothelial-derived relaxing factor)



- Furchgott and Zawadski Nature 1980:288:373-376

EDRF and Nitric Oxide (1987)





- Palmer, Ferrige, Moncada Nature 1987;327:524-526

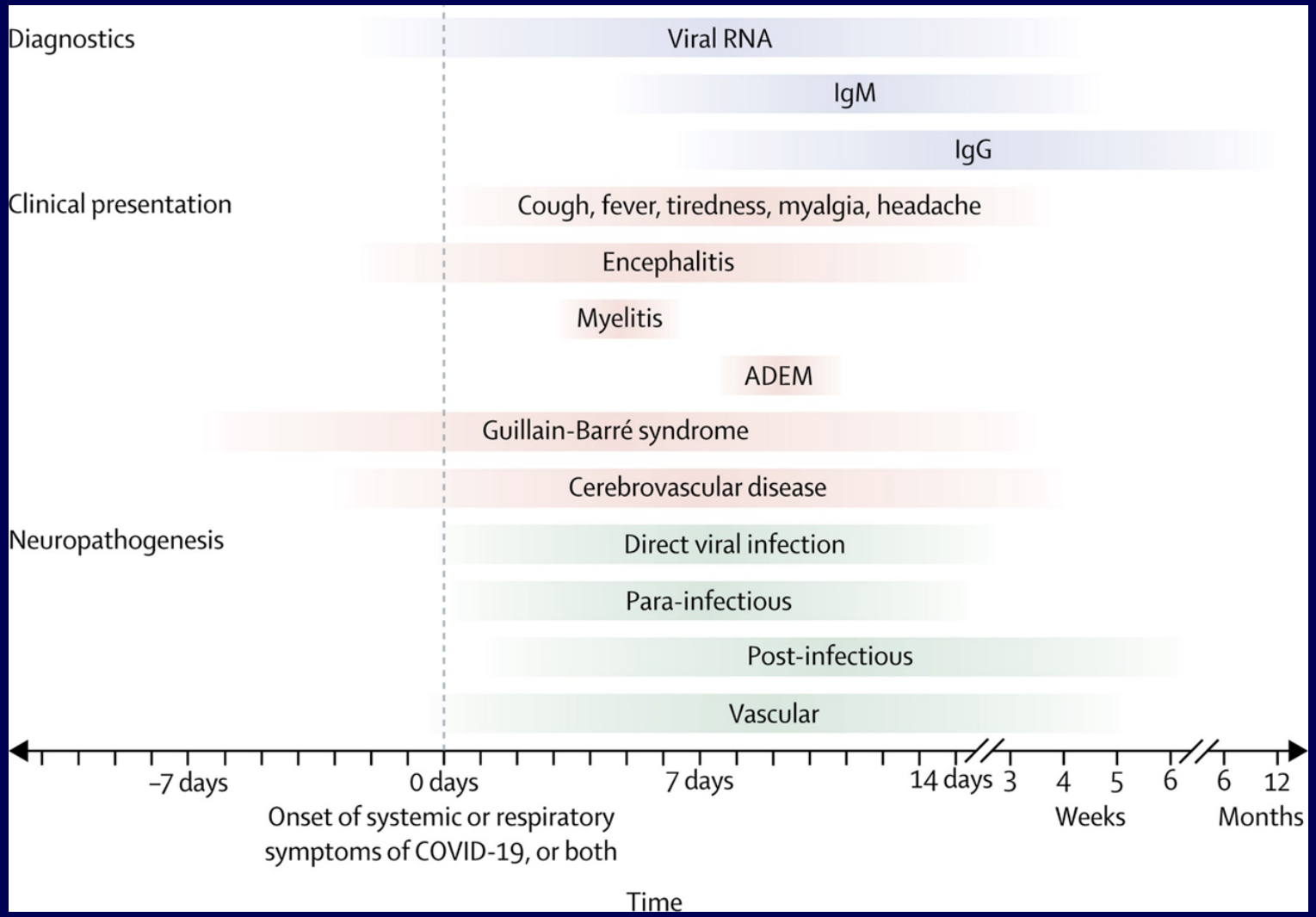
Neuropathophysiology

Illness from SARS-CoV-2 can provoke states that increase risk of neurological disease. The pathophysiology of the various neurological manifestations of COVID-19 is currently unknown

Wu, Brain Behav Immun, 2020

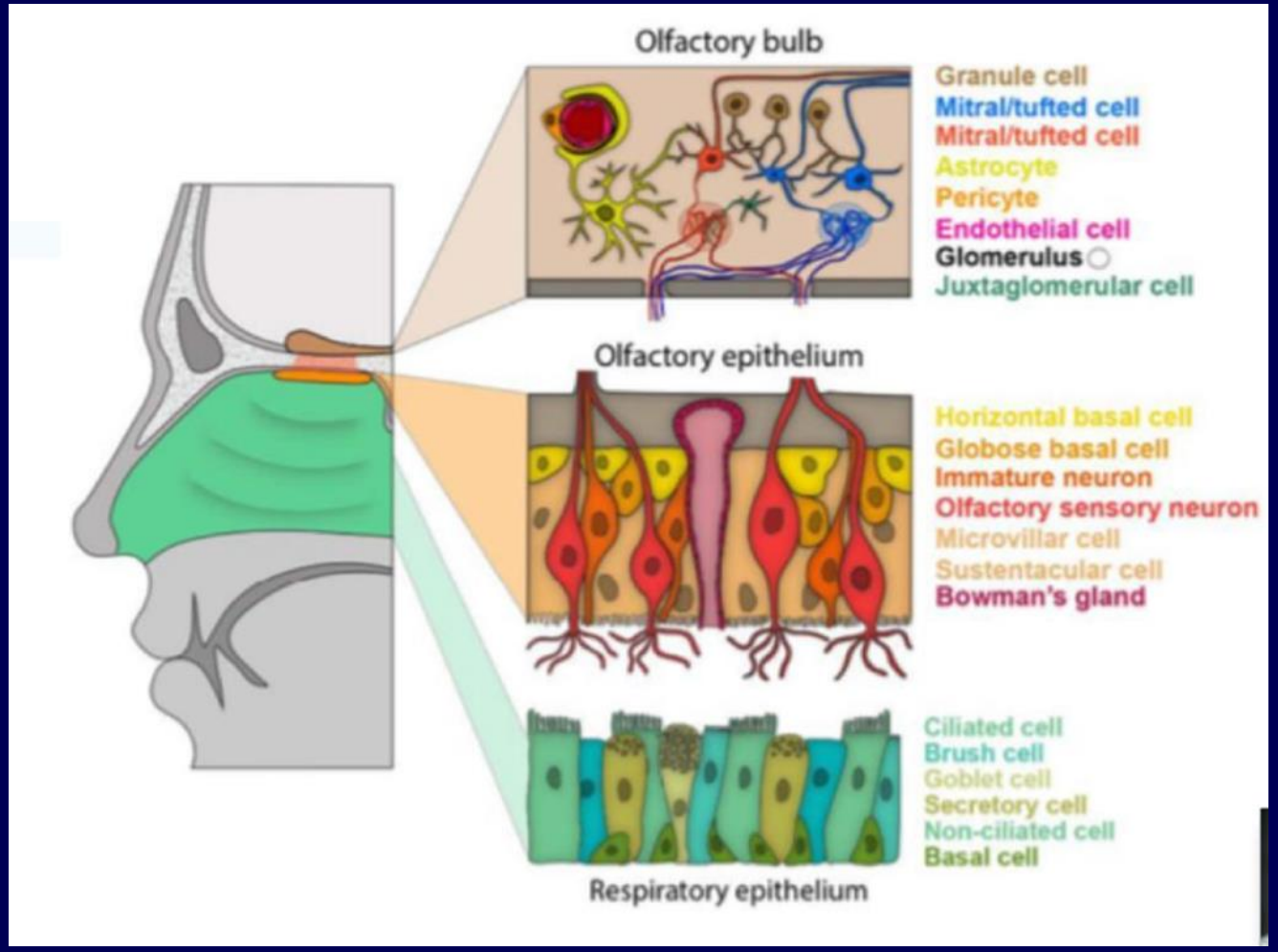
Roman et al JNS, 2020

Pathogenesis



Neurological associations of COVID-19
Mark A Ellul et al.Lancet Neurology
DOI: 10.1016/S1474-4422(20)30221-0

Anosmia and Probable cell targets: Respiratory epithelium, Olfatory epithelium and Olfatory bulb



Pathophysiology

- 6. Endotheliopathy (endothelitis)
- 7. Prothrombotic state /Embolism

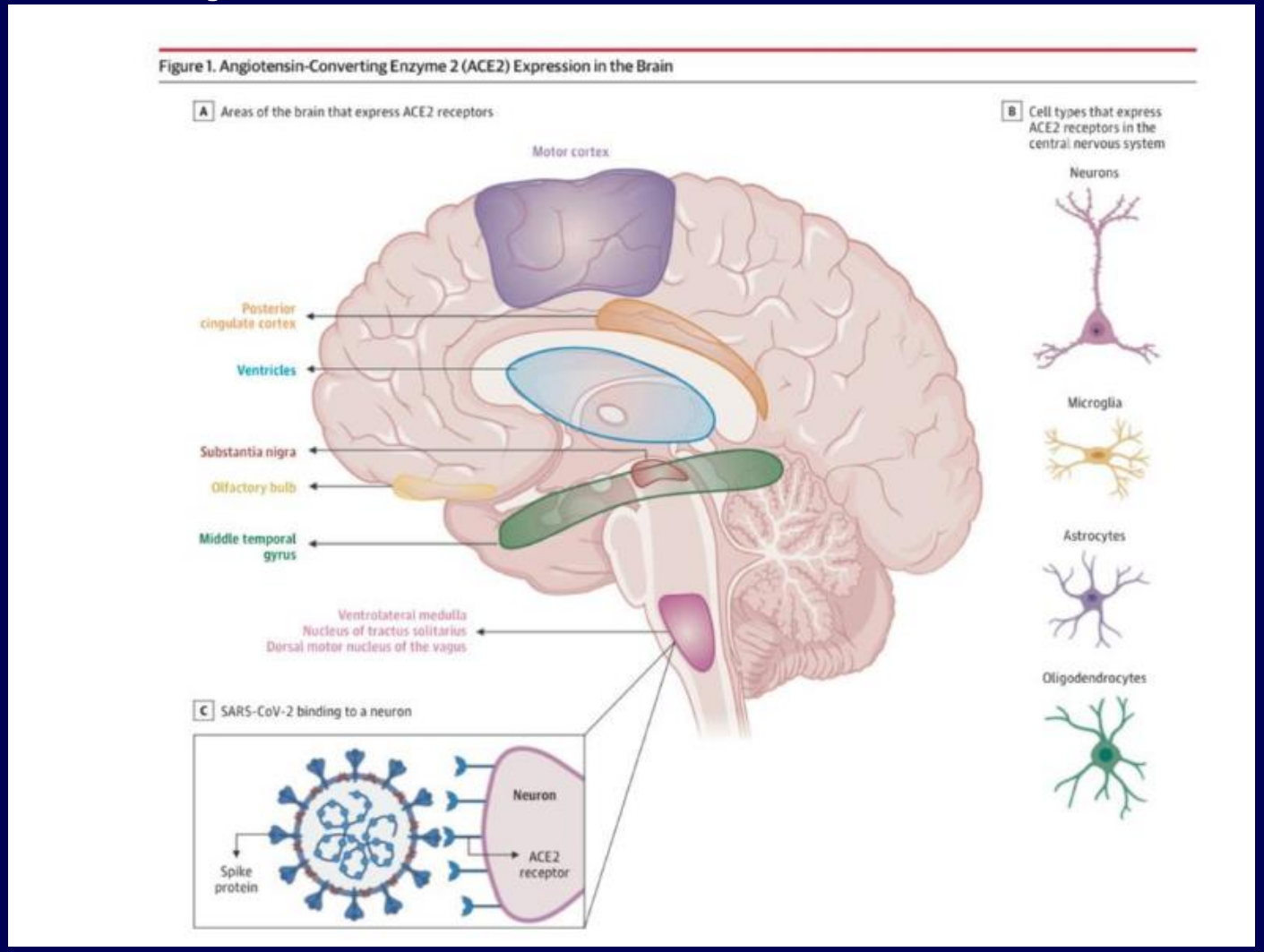
Roman et al JNS, 2020

Pathophysiology

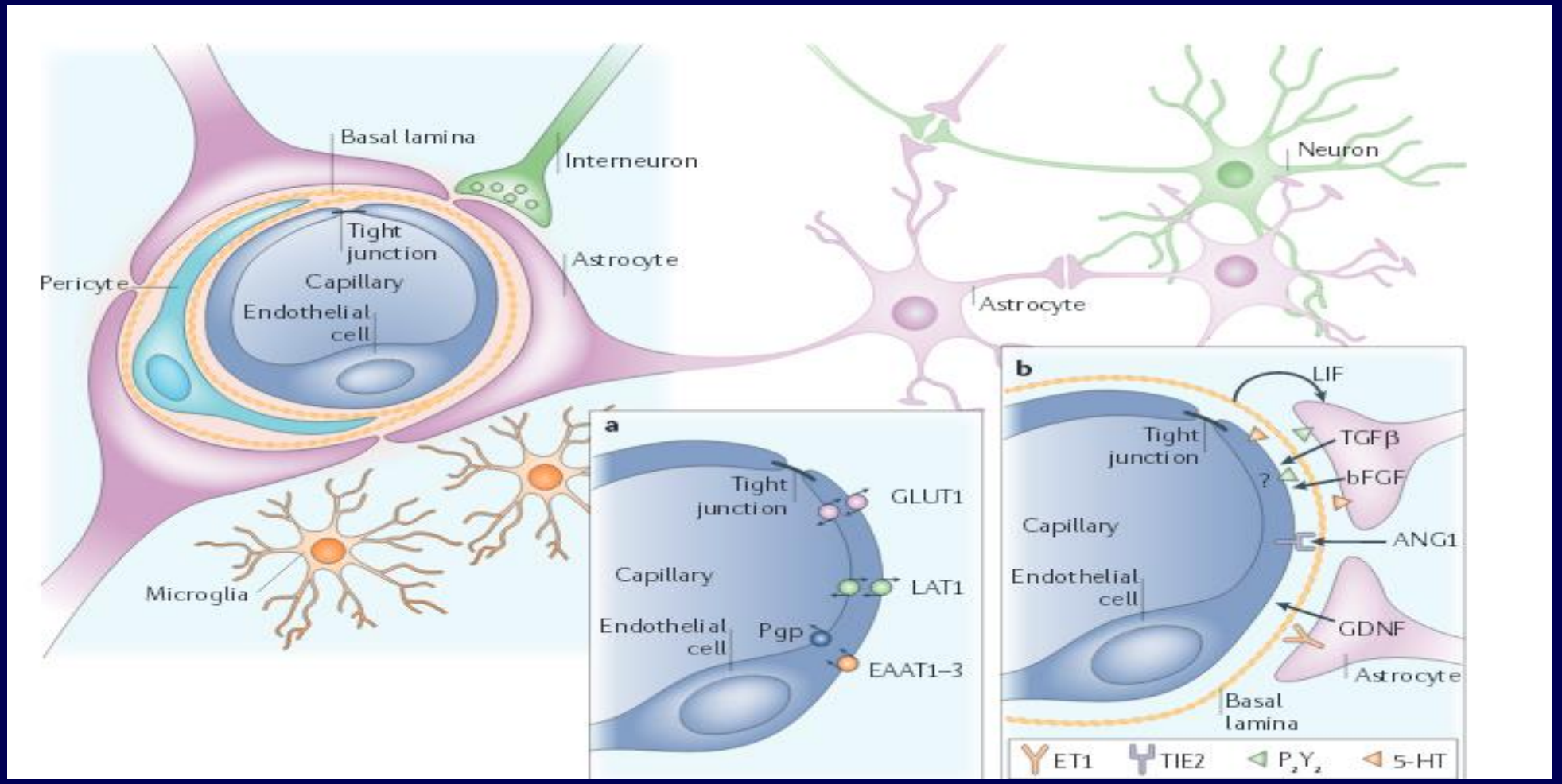
1. Direct viral invasion of the nervous system
2. Autoimmune sequelae
3. Hypoxia-mediated injury
4. Sequelae of the systemic proinflammatory state
5. Theoretical possibility of blood-brain barrier disruption secondary to SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2)

Roman et al JNS, 2020

Angiotensin-Coverting Enzyme expression in the Brain



Cerebral Endothelium (BHE)



- **Chow BW, Gu C. The Molecular Constituents of the Blood-Brain Barrier. Trends in Neurosciences 2015; 38:598-608.**

3. Acute Manifestations and Complications of Covid-19

Journal of the Neurological Sciences 414 (2020) 116884

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journal homepage: www.elsevier.com/locate/jns

Review Article

The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries

Gustavo C. Román[a,b,*], Peter S. Spencer[c], Jacques Reis[d], Alain Buguet[e], Mostafa El Alaoui Faris[f], Sarosh M. Katrak[g], Miguel Láinez[h], Marco Tulio Medina[i], Chandrashekhar Meshram[j], Hidehiro Mizusawa[k], Serefnur Öztürk[l], Mohammad Wasay[m], on behalf of the WFN Environmental Neurology Specialty Group

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[f] World Congress of Neurology, Marrakesh WCN2011, Moroccan Foundation Against Neurological Disease, Neurology, Mohammed V University of Rabat, Rabat, Morocco
[g] Neurology Department, Jaslok Hospital & Research Center, Professor Emeritus GMC and Sir JJ Group of Hospitals, Mumbai, India
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[j] Indian Academy of Neurology. Nagpur, India
[k] World Congress of Neurology, Kyoto WCN2017, National Center of Neurology and Psychiatry (NCNP), Japan, Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo, Japan
[l] Turkish Neurological Society, Department of Neurology, Selcuk University Faculty of Medicine, Konya, Turkey
[m] Pakistan International Neuroscience Society, Neurology, Aga Khan University, Karachi, Pakistan

Incidence

- Neurologic manifestations may occur in 36.4%-69% of hospitalized COVID-19 patients

Mao, JAMA Neurology, 2020

Helms, NEJM, 2020.

Acute neurologic manifestations

1. Delirium, confusion, or executive dysfunction (Helms, NEJM, 2020).
2. Smell or taste abnormalities (5-98%)
3. Headache (6.5-71%,)
4. Corticospinal tract signs (67%) (Helms, NEJM, 2020)
5. Dizziness (16.8%) (Mao, JAMA Neurology, 2020)

https://covidprotocols.org/protocols/neurology/

Acute neurologic complications

6. Stroke (2.5-5%)

7. GBS, Miller Fisher syndrome

8. Encephalitis, acute necrotizing encephalopathy, myelitis, CNS demyelinating lesions

https://covidprotocols.org/protocols/neurology/

Acute Neurologic Manifestations

The Neurology of COVID-19 due to SARS-CoV-2.

Neurologic diagnosis	*Features*	*City/Country*	*Author [Ref]*
Central nervous system symptoms			
Headache	6% to 8% (all patients)	Wuhan, China	Various [66,68,69]
	6.5% (all patients)	Beijing, China	Tian et al. [70]
	13% (stroke patients)	Wuhan, China	Chen et al. [71]
			Li et al. [62]
Agitation & Delirium	69% agitation (58 ICU patients)	Strasbourg, France	Helms et al. [91]
	65% delirium (58 ICU patients)		
	67% pyramidal tract signs		
Impaired Consciousness	22% (fatal cases vs. 1% non-fatal cases)	Wuhan, China	Chen et al. [71]
	14.8% (severe cases vs. 2.4% non-severe cases)	Wuhan, China	Mao et al. [3]
Anosmia, hyposmia	5.1% (cases from 3 hospitals)	Wuhan, China	Mao et al. [3]
	85.6% (cases from 12 hospitals)	Europe	Lechien et al. [4]
Dysgeusia	5.6% (cases from 3 hospitals)	Wuhan, China	Mao et al. [3]
	88% (cases from 12 hospitals)	Europe	Lechien et al. [4]

- Roman et al. Journal of the Neurological Sciences 2020

Cerebro vascular disease and Frontotemporal hypoperfusion

Central nervous system diseases			
Cerebrovascular Disease	2.4% (6/214)	Wuhan, China	Mao et al. [3]
	Ischemic stroke 5	Wuhan, China	Li et al. [62]
	Hemorrhagic stroke 1	China (6 case-series)	Aggarwal et al. [84]
	5.8% (13/221)		Helms et al. [91]
	Large-vessel ischemic stroke 11	Strasbourg, France	Oxley et al. [129]
	Hemorrhagic stroke 1	New York, US	
	Cerebral sinus thrombosis 1		
	1% to 6% (pooled analysis)		
	23% (3/13 ICU patients from 2 hospitals)		
	Ischemic strokes 3		
	Large-vessel ischemic strokes		
Frontotemporal hypoperfusion	58 ICU patients with severe COVID-19, 45 survived (33% had frontal lobe behavioral signs)	Strasbourg, France	Helms et al. [91]
	11/11 CBF-ASL-MRI frontotemporal hypoperfusion		

- Roman et al. Journal of the Neurological Sciences 2020

Thrombosis, Subarachnoid Hemorrhage and Acute Hemorrhagic Necrotizing Encephalopathy

Arterial & Venous Thromboses	184 patients from 3 hospitals	The Netherlands	Klok et al. [92]
	31% thrombotic complications including pulmonary embolism in 81%	China	Zhang et al. [93]
	27% venous thromboses	Zurich,	Varga et al. [36]
	3.7% arterial thromboses	Switzerland	
	3 patients with multiple arterial thromboses of legs, hands, brain, associated with anticardiolipin IgA and anti–β_2-glycoprotein-I IgA and IgG antibodies		
	3 patients with multiple arterial thromboses and multi-organ failure due to coronavirus attachment to ACE2 receptors, viral invasion of endothelial cells, resulting in lymphocytic endotheliitis		
Subarachnoid hemorrhage	1 patient with Immune thrombocytopenic purpura	France	Zulfiqar et al. [94]
Acute Hemorrhagic Necrotizing Encephalopathy	Brain MRI showed bilateral hemorrhagic rim-enhancing lesions in the thalami, medial temporal lobes, and subinsular regions, probably associated with cytokine	Detroit, USA	Poyiadji et al. [61]

- Roman et al. Journal of the Neurological Sciences 2020

Neurologic Complications

Meningoencephalitis	Seizures, neck rigidity, CSF pleocytosis (12/μ/L). CSF-RT-PCR positive for SARS-CoV-2.	Japan	Moriguchi et al. [102]
Encephalopathy	Decreased level of consciousness with COVID-19. Negative CSF & CT brain; EEG: diffuse encephalopathy	Florida, USA	Filatov et al. [103]
	Confusion, myalgias, meningeal signs, CSF opening pressure 220 mmHg, normal CT brain.	Wuhan, China	Ye et al. [104]
Seizures	Recurrent generalized tonic-clonic seizures; normal CT/MRI, CSF-RT-PCR negative for SARS-CoV-2	Iran	Karimi et al. [105]
Myelitis	COVID-19 pneumonia, high fever (40 °C), acute flaccid paraplegia	Wuhan, China	Zhao et al. [113]

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Neurologic Complications

Peripheral nervous system & muscle			
Neuritic pain	8.9%	Wuhan, China	Mao et al. [3]
Guillain-Barré syndrome	First case in China 61-year-old woman	Shanghai, China	Zhao et al. [108]
	First case in USA 54-year-old man	USA	Virani et al. [109]
	Three cases from northern Italy	Italy	Toscano et al. [110]
Miller Fisher Syndrome, Polyneuritis Cranialis	50-year-old man with diplopia due to external ophthalmoplegia, ataxia and areflexia	Madrid, Spain	Gutiérrez-Ortiz et al. [112]
Neurosensory hearing loss	39-year-old man with diplopia from bilateral abducens palsy, global areflexia but no ataxia	Bangkok, Thailand	Sriwijitalai & Wiwanitkit [113]
	Old woman from Thailand		
Myalgia	36% early symptom in > 1200 COVID-19 patients	Wuhan, China	Several
	26–51% muscle fatigue	Wuhan, China	[62,68,69] Huang et al. [63]

- Roman et al. Journal of the Neurological Sciences 2020

Neurologic Complicactions

			Huang et al. [63]
Myopathics	10.7% (19.3% severe vs. 4.8% non-severe)	Wuhan, China	Mao et al. [3].
Rhabdomyolysis	33% have increased creatine kinase	China	Several [64–66]
	Early sign in 2 case reports	Wuhan, China	Jin & Tong [121]
			Suwanwongse et al. [122]
Irreversible respiratory failure			
Case-fatality rates (CFR)	81% of 72,314 COVID-19 infections are mild but 20% or 8255 are severe (CFR 8.0% - 14.8%) or critical (CFR 49%)	China	Wu & McGoogan [124]
		Worldwide	Several [67,69,74,80,106]
	Neurogenic respiratory failure due to viral brainstem invasion could explain the dismal prognosis		

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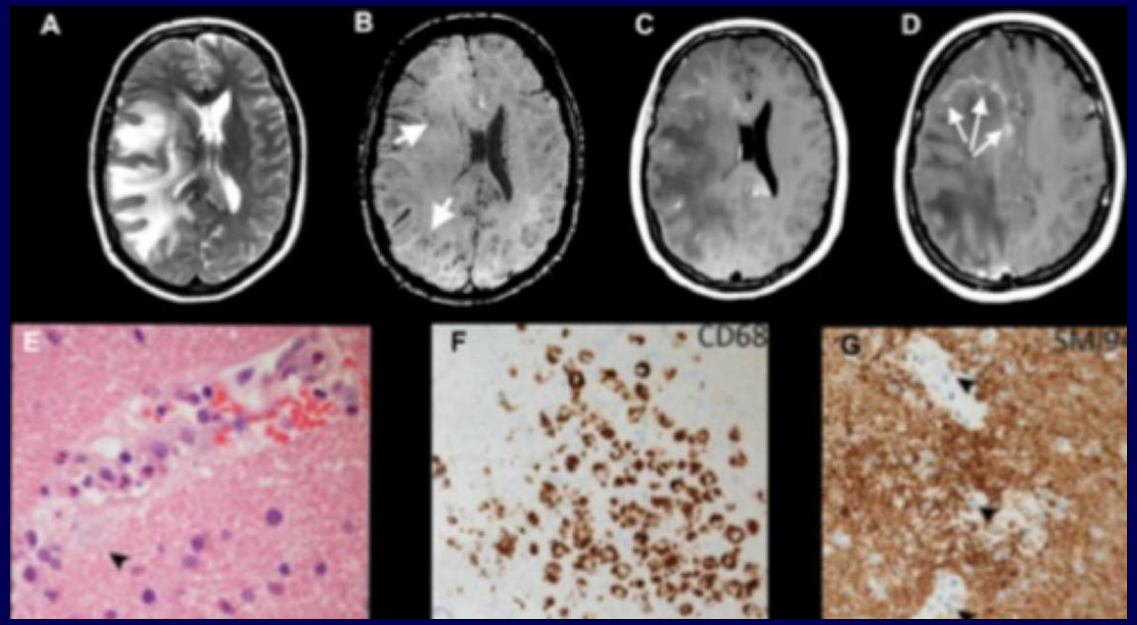
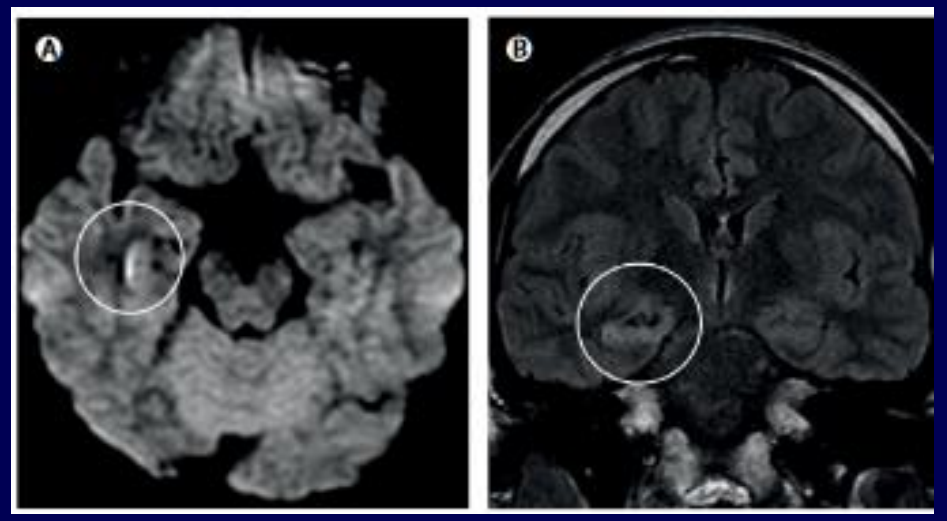
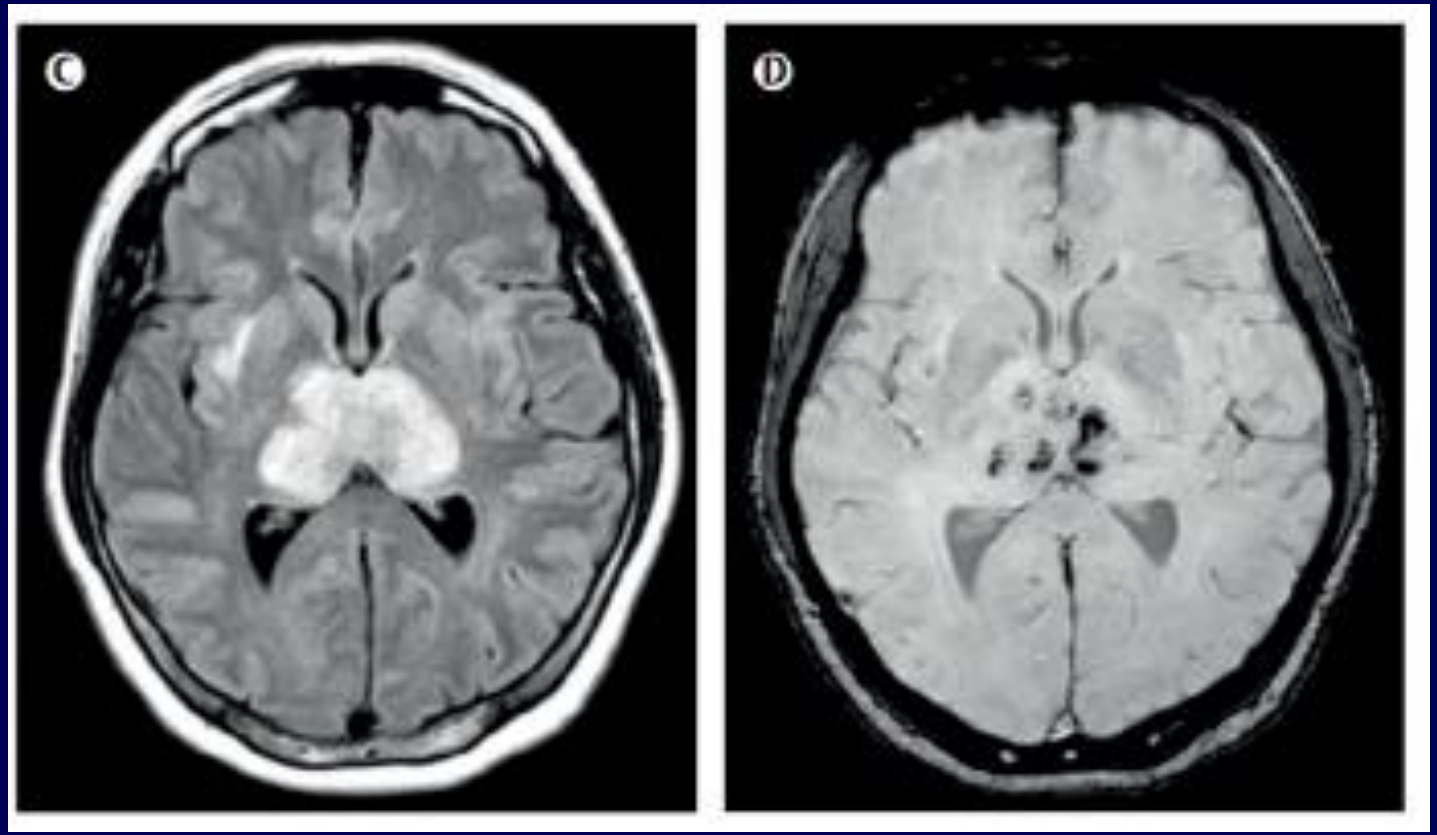
Encephalitis COVID 19





Ellul et al. Lancet Neurol 2020DOI:https://doi.org/10.1016/S1474-4422(20)30221-0

Acute Necrotizing encephalitis COVID 19



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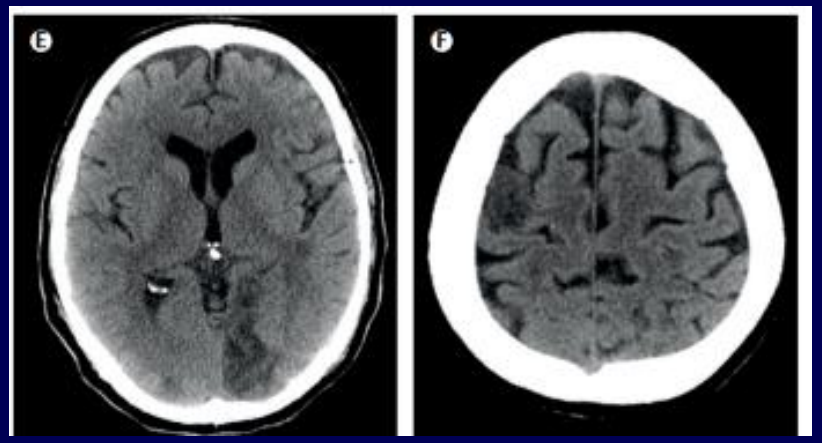
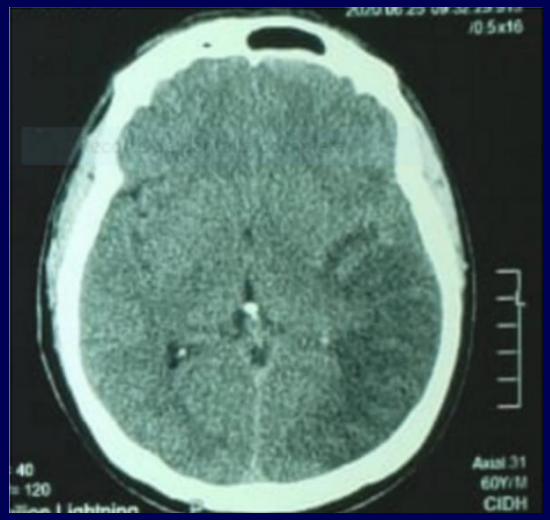
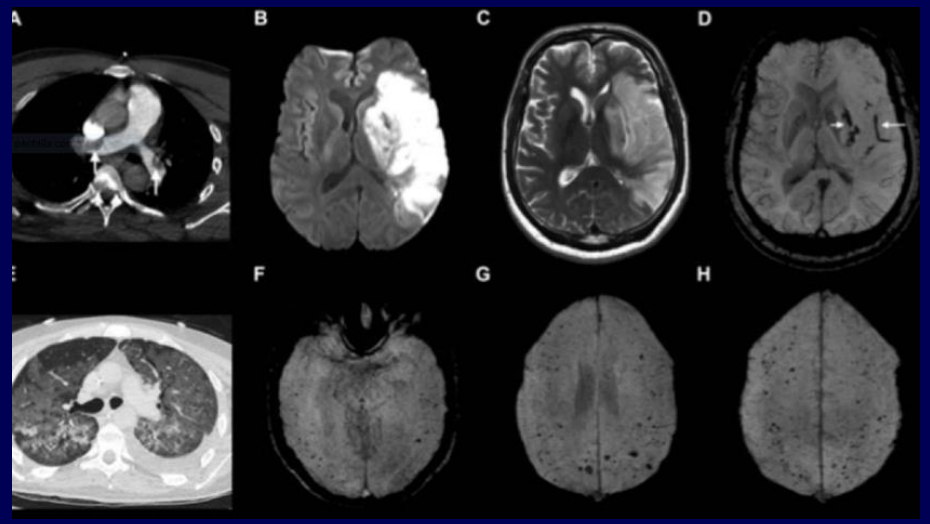
COVID 19 Stroke







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	Total (n=1733)	Seven-category scale			OR or β (95% CI)	
		Scale 3: not requiring supplemental oxygen (n=439)	Scale 4: requiring supplemental oxygen (n=1172)	Scale 5–6: requiring HFNC, NIV, or IMV (n=122)	Scale 4 vs 3	Scale 5–6 vs 3
ymptoms						
Any one of the following symptoms	1265/1655 (76%)	344/424 (81%)	820/1114 (74%)	101/117 (86%)	OR 0·70 (0·52 to 0·96)*	OR 2·42 (1·15 to 5·08)*
Fatigue or muscle weakness	1038/1655 (63%)	281/424 (66%)	662/1114 (59%)	95/117 (81%)	OR 0·74 (0·58 to 0·96)*	OR 2·69 (1·46 to 4·96)*
Sleep difficulties	437/1655 (26%)	116/424 (27%)	290/1114 (26%)	31/117 (26%)	OR 0·92 (0·71 to 1·21)	OR 1·15 (0·68 to 1·94)
Hair loss	359/1655 (22%)	93/424 (22%)	238/1114 (21%)	28/117 (24%)	OR 0·99 (0·74 to 1·31)	OR 1·17 (0·67 to 2·04)
Smell disorder	176/1655 (11%)	55/424 (13%)	107/1114 (10%)	14/117 (12%)	OR 0·69 (0·48 to 1·00)	OR 0·90 (0·43 to 1·87)
Palpitations	154/1655 (9%)	45/424 (11%)	96/1114 (9%)	13/117 (11%)	OR 0·86 (0·58 to 1·28)	OR 1·31 (0·61 to 2·80)
Joint pain	154/1655 (9%)	51/424 (12%)	86/1114 (8%)	17/117 (15%)	OR 0·56 (0·38 to 0·83)*	OR 0·74 (0·36 to 1·50)
Decreased appetite	138/1655 (8%)	42/424 (10%)	85/1114 (8%)	11/117 (9%)	OR 0·84 (0·56 to 1·27)	OR 1·56 (0·71 to 3·43)
Taste disorder	120/1655 (7%)	37/424 (9%)	75/1114 (7%)	8/117 (7%)	OR 0·84 (0·54 to 1·30)	OR 0·80 (0·32 to 2·02)
Dizziness	101/1655 (6%)	32/424 (8%)	60/1114 (5%)	9/117 (8%)	OR 0·77 (0·48 to 1·22)	OR 0·95 (0·39 to 2·31)
Diarrhoea or vomiting	80/1655 (5%)	27/424 (6%)	48/1114 (4%)	5/117 (4%)	OR 0·71 (0·42 to 1·22)	OR 0·39 (0·11 to 1·42)
Chest pain	75/1655 (5%)	19/424 (4%)	46/1114 (4%)	10/117 (9%)	OR 0·94 (0·52 to 1·67)	OR 2·55 (0·99 to 6·62)
Sore throat or difficult to swallow	69/1655 (4%)	20/424 (5%)	44/1114 (4%)	5/117 (4%)	OR 0·91 (0·50 to 1·65)	OR 1·21 (0·40 to 3·73)
Skin rash	47/1655 (3%)	16/424 (4%)	27/1114 (2%)	4/117 (3%)	OR 0·64 (0·32 to 1·26)	OR 0·71 (0·18 to 2·87)
Myalgia	39/1655 (2%)	11/424 (3%)	24/1114 (2%)	4/117 (3%)	OR 0·80 (0·38 to 1·69)	OR 1·72 (0·47 to 6·27)
Headache	33/1655 (2%)	10/424 (2%)	20/1114 (2%)	3/117 (3%)	OR 0·76 (0·35 to 1·69)	OR 1·53 (0·36 to 6·52)
Low grade fever	2/1655 (<1%)	1/424 (<1%)	1/1114 (<1%)	0	NA	NA

Post-Covid Fatigue Syndrome and postural tremor (63 y/o Honduran male)

Post-Fatigue Covid Syndrome and Mild Cognitive Impairment, a 43 y/o female

Conclusions

- 1. Several neuropathologic mechanisms are associated with the Covid-19 infections (for example vascular damage, direct, para and post-infection involvement)
- 2. The neurologic complications of Covid-19 are heterogeneus and have high incidence (30 to 69%)
- 3. Post-covid fatigue syndrome represents 63% of the Long Covid -19 manifestations.